REMARKS

Applicants wish to thank Examiner Purdy and Examiner Landau for conducting a telephonic interview with Applicants' undersigned representative on September 21, 2009 to discuss the amendments to the claims and the outstanding rejections.

Applicants have cancelled claim 83 without prejudice expressly reserving the right to pursue the subject matter of the cancelled claims in one or more subsequently file applications.

Applicants have amended claim 71 to depend on claim 80 to correct a clerical error.

Applicants have amended claims 80 and 82 to recite "500mg clarithromycin" and amended claim 84, to depend on claim 80 and to recite 350 mg glycerol behenate and 150mg low viscosity hydroxypropyl methylcellulose. Support for these amendments is found in Examples 1-5.

Claims 70-72 and 76-84 stand rejected under 35 U.S.C. §112, first paragraph for purportedly lacking written description. Applicants disagree for the reasons of record but in view of the amendments to the claims request that the Office reconsider and withdraw the rejection.

The present claims 80, 82 and 84 recite 500mg of a clarithromycin component, or derivative thereof. Claim 84 also recites, 350 mg glycerol behenate and 150mg low viscosity hydroxypropyl methylcellulose. Express support for these amendments is found in, e.g., the Examples. Applicants have provided the necessary showing to support adequate written description of the current claims and request that the Office withdraw the rejection of the claims under 35 U.S.C. §112, first paragraph

Claims 70-72 and 76-84 stand rejected under 35 U.S.C. §103(a) for purportedly being unpatentatble over Akiyama in view of WO 98/14176 ("Farah"), US equivalent Patent No. 6,194,005. Applicants disagree.

In In Re Kubin (Fed Cir 2009), the court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under § 103. In the first class:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. ... In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.

This class of impermissible "obvious to try" situations is particularly applicable to Applicants' claimed invention.

Akiyama teaches broad genera of compounds and broad genera of their weight percentages, including, e.g.:

> a swelling material that swells a viscogenic agent or accelerates the swell of a viscogenic agent caused by water (page 15, lines 16-19), in an amount of about 0.5 to 50 weight % (page 15, line 25-27)
>
> any type of viscogenic agent (page 17, lines 11-15), preferably having a viscosity of 3 to 50,000cps (page 17, lines 20-22), in amounts of about 0.005 to about 99% (page 19, lines 5-7),
>
> a polyglycerol fatty acid ester in an amount of 5-98% (page 12, lines 1-2),
>
> a antimicrobial substance in an amount of 0.0005-95% (page 26, lines 13-15),
>
> an optional coating material, and

surfactants.

Akiyama further teaches that the selection of polyglycerol fatty acid ester is dependent on many factors, including the ***identity of the active compound*** and viscogenic agent.

> "the proper polyglycerol fatty acid ester can be selected with reference to the particular active ingredient (e.g., anti-HP agent, etc.), viscogenic agent, swelling material (e.g., curdlan, and/or low-substituted hydroxypropylcellulose, etc.), the particular combination thereof, and the objective form of the composition"
>
> (sentence spanning page 10-11).

Thus, Akiyama fails to provide the necessary direction as to which of many possible choices of polyglycerol fatty acid esters is likely to be successful with particular active ingredients.

Farah teaches that their preparation method and the composition of the formulation could either ***enhance or inhibit*** the release of an active agent, depending on the active agent. Farah does not prepare any formulations with clarithromycin and does not present any analysis of formulations comprising any combination of glyceryl behenate and clarithromycin. Thus one of skill in the art could not predict whether Farah's preparation method and formulation would successfully either enhance, inhibit or have no effect on the release of clarithromycin.

Therefore given that Akiyama teaches that one of the many factors that influences the selection of polyglycerol fatty acid ester is the active ingredient, but does not suggest which of many possible choices of polyglycerol fatty acid esters available in the art is likely to be successful, and given that Farah fails to prepare a formulation of clarithromycin with glyceral behenate and Farah teaches that their preparation method and formulation could either enhance or

inhibit the release of an active agent, one of skill in the art would not be directed to a glyceral behenate for combination with clarithromycin and could not predict how any composition comprising glyceral behenate and clarithromycin would behave.

Furthermore, Applicants' claims require a low viscosity HPMC at 13-18 weight percent. Akiyama's teaching that the viscogenic agent "may be selected from any agent that is capable of swelling in water." does not provide any sort of guidance as to which agent one should use. Akiyama's more specific teaching that "a suitable synthetic polymer has a viscosity 3-50,000cps and a basic or acidic polymer has a viscosity of about 100 to about 50,000cps" (see page 17, lines 20-22 and lines 24-28) is also insufficient to guide one of skill in the pharmaceutical arts to the particular claimed controlled release formulation comprising the particular amounts of (i) low-viscosity HPMC, (ii) glyceral behenate and (iii) clarithromycin recited in Applicants' claims.

In addition, the Office previously cited Evenstad for teaching that high viscosity HPMCs are useful for sustaining action. Evenstad supports Applicants' position that one of skill in the art considering all that is available in the pharmaceutical arts would not be motivated to use a low viscosity as opposed to a high viscosity HPMC for the formulations in view of Akiyama's general disclosure.

Given the broad scope of Akiyama's recited genera, even if Akiyama's polyglycerol fatty acid were substituted by a glyceral behenate, combining Akiyama's genera of materials and material amounts, e.g.,

> a swelling material that swells a viscogenic agent or accelerates the swell of a viscogenic agent caused by water (page 15, lines 16-19), in an amount of about 0.5 to 50 weight % (page 15, line 25-27)
>
> any type of viscogenic agent (page 17, lines 11-15), preferably having a viscosity of 3 to 50,000cps (page

17, lines 20-22), in amounts of about 0.005 to about 99% (page 19, lines 5-7),

a polyglycerol fatty acid ester in an amount of 5-98% (page 12, lines 1-2),

a antimicrobial substance in an amount of 0.0005-95% (page 26, lines 13-15),

an optional coating material, and

surfactants.

would present countless formulation permutations comprising any combination of (i) 5-98% glyceral behenate, (ii) 0.5 to 50 weight % of any swelling material that swells a viscogenic agent or accelerates the swell of a viscogenic agent caused by water, (ii) 0.005 to about 99% of any type of viscogenic agent, preferably having a viscosity of 3 to 50,000cps, and (iii) any antimicrobial substance in an amount of 0.0005-95%. One of skill in the art could not reasonably predict which of those permutations would be a suitable controlled release formulation for clarithromycin. One of skill in the pharmaceutical arts would essentially be throwing metaphorical darts at a board filled with combinatorial prior art possibilities to reach Applicants' claimed invention, which is just the situation that the court in In re Kubin (Fed Cir 2009), warned against when evaluating an invention for obviousness. As such, the combination of Akiyama and Farah fail to render Applicants' claimed formulation obvious.

In view of the forgoing remarks and amendments to the claims, Applicants request that the Office reconsider and withdraw the rejection of the claims under 35 U.S.C. §103 over Akiyama in view of Farah.

Claims 71, 72, 76-78 and 80-83 stand rejected under 35 U.S.C. §103(a) for purportedly being unpatentable over Briskin in view of Gibson and Evenstad as evidenced by Methocel™ and Akiyama.

The Office concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of

Briskin, Gibson and Evenstad and specifically utilize a low viscosity HPMC. The Office also concludes that "one would have been motivated to substitute Briskin's hydrophilic binders (cellulose derivative HMC and Povidone) for instant cellulose derivative (HPMC) with a reasonable expectation of similar results since Gibson teaches that HPMC, HMC and Povidone are conventional hydrophilic binders utilized in pharmaceutical compositions" (Office Action page 13). Applicants disagree.

Those of skill in the art appreciate that different binders have different properties that confer different characteristics to pharmaceutical formulations and without a description of the properties of the three different binders in Briskin's formulation, i.e., Providone K90, a nondescript HPC and a nondescript Carbopol™, one of skill in the art would not be motivated to simply replace any of them with an HPMC with the expectation of similar effects.

Evidence that those of skill in the art do not consider all PVPs, HPCs and HPMCs to be functionally equivalent is found in Evenstad, which states "hydroxypropylmethylcelluloses vary in their viscosity, methoxy content and hydroxypropoxyl content. Properties also vary." (Col. 3, lines 5-7). Evidence that those of skill in the pharmaceutical arts do not consider all HPCs and all HPMCs to be functionally equivalent is found in Akiyama who distinguishes "low-substituted HPC" from other HPCs and HPMCs by describing "low-substituted HPC" as "a material which swells a viscogenic agent" (see page 15, lines 16-24) and then describing viscogenic agents to include Carbopol™, HPC and HPMC. Evenstad also teaches the different functionality of high viscosity versus low viscosity HPMCs, as acknowledged by the Office in the Action of July 30, 3008, page 11, "Evenstad teaches the use of high viscosity to provide sustained release whereas a water-soluble binder such an HPMC having binding properties has a much lower viscosity; typically a viscosity of less than 100cps such as Methocel E15. See col. 3, lines 5-67." Thus, not all HPCs and HPMCs are functionally equivalent.

One of skill in the pharmaceutical arts could not reasonably predict the effect that substituting an HPMC for one or more of PVPK90, the uncharacterized HPC and the uncharacterized Carbopol™ would have on the characteristics of Briskin's formula 1b. Without any description of the HPC's and the Carbopol™'s properties, one in the pharmaceutical arts could not determine which one of a variety of compounds could be substituted for the Briskin binders and still maintain the characteristics of formula 1b.

As discussed above, Evenstad and Akiyama demonstrate that all HPCs and HPMCs are not functionally equivalent and thus without a description of the HPCs and Carbopol™ in Briskin's formula 1b, the skilled artisan would not simply replace one or more of Briskin's "binders" with just another "binder" and expect to obtain similar results.

Furthermore, even if one of skill in the pharmaceutical arts were motivated to substitute the "conventional binders" of Briskin's formula 1b with HPMC then the modified formula 1b would comprise 36% HPMC, not 10.5% HPMC. This is because, at the time of this invention those of skill in the art appreciated that Carbopol™ is also a binder, see e.g., U.S. Patent No. 4,184,888, which states

> "To further facilitate tableting, a conventional tableting binder may optionally be employed . . . . Suitable binders include, . . . hydroxypropylmethyl cellulose . . . or a carboxypolymethylene polymer (carbomer)."
>
> Col. 3, lines 47 to 54.

Carbopol™ is a carbomer and therefore Carbopol™ a conventional binder. Thus, Briskin teaches a formulation comprising a "binder" in a total weight percent of 36.5% (5.5% Povidone, 5% HPC and 26% Carbopol™), which is twice the maximum amount of HPMC recited in Applicants' claims.

Furthermore, Evenstad is directed to improved controlled release formulations and Evenstad's solution to making a controlled release formulation is to use a high viscosity HPMC to achieve controlled or sustained release. Thus, Evenstad teaches away from using a low viscosity HPMC to produce a controlled release formulation, as required in Applicants' claims.

> . "When the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely non-obvious ...."
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> *KSR Int'l Co. v Teleflex Inc.*
> 550 U.S. __ (2007).

The foregoing remarks demonstrate that considered within the context of the state of the art at the time of filing, the combination of Briskin, Gibson, and Evenstad as evidenced by Methocel™ fails to teach or suggest the invention as claimed.

Applicants request the Office to reconsider and to withdraw the rejection of claims 71, 72, 76-78 and 80-83 under 35 U.S.C. §103 over Briskin in view of Gibson and Evenstad as evidenced by Methocel™.

If there are any questions regarding this response or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket # 104101.B700017).

Respectfully submitted,

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